F ENT COOPERATION TREA

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

REES, Marion, L.
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP
ROYAUME-UNI

Date of mailing (day/month/year)
12 July 2001 (12.07.01)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
PG3692

International application No.
PCT/EP00/05029

International filing date (day/month/year)
02 June 2000 (02.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

REES, Marion, L.
Glaxo Wellcome PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
United Kingdom

State of Nationality

State of Residence

Telephone No.
020 8966 8000

Facsimile No.
020 8966 8838

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

REES, Marion, L.
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP
United Kingdom

State of Nationality

State of Residence

Telephone No.
020 8966 8412

Facsimile No.
020 8966 8838

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

F. Baechler

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

REC'D 21 SEP 2001

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG3692		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05029	02/06/2000	01/07/1999
International Patent Classification (IPC) or national classification and IPC C12N5/00		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/01/2001	19.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seranski, P Telephone No. +49 89 2399 7846

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05029

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1-5 as originally filed

Drawings, No.:

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	14
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Re Item V: Novelty, Inventive Step and Industrial Applicability (Art. 33(2) and (3) PCT)

1.1 Reference is made to the following document:

D1: CHANG HO NAM ET AL: 'High density cell culture membrane-based cell recycle.' BIOTECHNOLOGY ADVANCES, vol. 12, no. 3, 1994, pages 467- 487, XP000978939 ISSN: 0734-9750

1.2 Claim 14 is not new in view of document D1, thus not fulfilling the requirements of Art. 33(2) PCT. Claim 14 attempts to seek protection for a hollow fibre bioreactor, wherein the method of the preceding claims 1-13 is carried out.
In document D1, also a hollow-fibre bioreactor is disclosed that is used for high density cell culture. The same reactor can also be used for the application of the methods as claimed in the present application. The bioreactor is not rendered novel only because it is used in a special cell culture procedure. Moreover, it is an implicit technical feature of the hollow-fibre bioreactor of D1 that the methods of the present application can be carried out in said bioreactor, regardless if the method as such is novel and inventive. Beside this, hollow-fibre reactors are also known from WO9527040 and EP-A-0 317 874.

1.3 The prior art teaches only continuos cell culture systems in hollow-fibre reactors, for example for the cultivation of cell lines for the production of monoclonal antibodies or secondary metabolites. The difference of the present invention compared to the prior art lies in the infection of the cell line that is already in culture within the hollow-fibre reactor and the subsequent multiplying of infected cells, whereafter harvesting of the infected cells non-infected cell give rise to re-population of the reactor. The advantage of the present invention lies in the continuos culturing of the cell line followed by a greater productivity of the cells. The underlying technical problem lies in the provision of a method for continuously culturing cell lines that survive infections with lytic organisms that are capable of repopulating a bioreactor after harvesting infected cells. This problem has been solved by the present application. The prior art does not teach

the solution of the present invention. In consequence, the method of claims 1-13 fulfil the requirements of inventive step (Art.33(3) PCT).

1.4 Claims 1-14 fulfil the requirements of Industrial Applicability (Art.33(4) PCT).

2. Re Item VIII: Clarity (Art. 6 PCT)

2.1 Claims 1 lacks clarity as required by Art. 6 PCT, because the Applicant tries to define the subject matter for which protection is sought by the result to be achieved. Independent claim 1 does not contain all the technical features essential to the definition of the invention. From the reading of the claim the borders of the scope of the protected subject matter are not clear to the skilled person because of the vague wording, i.e. that the cell 'can' be harvested and 'can' survive.

2.2 It is clear from the description on pages 7-8 that the following features are essential to the definition of the invention:

(1) The stable cell line is capable of growing in the extra capillary space of the bioreactor to establish a population from at least 10e6 to10e9 cells per ml.
(2) At the point of infection with the lytic organism, the cell density will be 10e6 cell per ml.

2.3 Since independent claim 1 does not contain these features it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

2.4 The wording in claims 5 and 6, stating that the cell line 'can survive for at least' renders the scope of the claims unclear, because it gives the skilled person no clear technical teaching insofar, as it is also possible that the cells could also survive less than the time period given in the claims, which implies, that also cell lines which are not intended to fall under the scope of present claims, are included.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02548 A2

(51) International Patent Classification[7]: C12N 5/00

(21) International Application Number: PCT/EP00/05029

(22) International Filing Date: 2 June 2000 (02.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915413.0 1 July 1999 (01.07.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FORD, Martin, James** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HISSEY, Paul, Henry** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **PATEMAN, Tony, James** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **REES, Marion, L.**; Glaxo Wellcome PLC, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/02548 A2

(54) Title: PROPAGATION METHOD

(57) Abstract: The present invention provides a method for the propagation of lytic organisms which comprises the infection of the cells of a stable cell line within a hollow fibre bioreactor with a lytic organism, wherein after said infection, said organism multiplies within the cells and can be harvested, characterised in that the cell line can survive for at least ten days after said infection. The invention further provides a method as herein described wherein after harvest, the cell line is allowed to re-populate the bioreactor, and at least one subsequent harvest may be taken, with the cell line being able to re-populate the bioreactor after each harvest.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02548 A3

(51) International Patent Classification[7]: C12N 7/00, 15/85, C12M 3/00, C07K 14/00, C12N 9/00, 9/02

(21) International Application Number: PCT/EP00/05029

(22) International Filing Date: 2 June 2000 (02.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915413.0 1 July 1999 (01.07.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FORD, Martin, James** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HISSEY, Paul, Henry** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **PATEMAN, Tony, James** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **REES, Marion, L.**; Glaxo Wellcome PLC, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
12 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/02548 A3

(54) Title: METHODS FOR THE PROPAGATION OF LYTIC ORGANISMS

(57) Abstract: The present invention provides a method for the propagation of lytic organisms which comprises the infection of the cells of a stable cell line within a hollow fibre bioreactor with a lytic organism, wherein after said infection, said organism multiplies within the cells and can be harvested, characterised in that the cell line can survive for at least ten days after said infection. The invention further provides a method as herein described wherein after harvest, the cell line is allowed to re-populate the bioreactor, and at least one subsequent harvest may be taken, with the cell line being able to re-populate the bioreactor after each harvest.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

REES, Marion L.
GLAXOSMITHKLINE
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP
GRANDE BRETAGNE

21 SEP 2001

Corporate Intellectual Property
NEW HORIZONS COURT
RECEIVED
21 SEP 2001

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.09.2001
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PC36922	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05029	02/06/2000	01/07/1999

Applicant
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hingel, W Tel. +49 89 2399-8717

Form PCT/IPEA/416 (July 1992)

Express Mail Label No.
EL395895089US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG3692		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05029	02/06/2000	01/07/1999
International Patent Classification (IPC) or national classification and IPC C12N5/00		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the International application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/01/2001	19.09.2001
Name and mailing address of the internationa' preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seranski, P Telephone No. +49 89 2399 7846

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05029

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1-5 as originally filed

Drawings, No.:

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-13
	No:	Claims 14
Inventive step (IS)	Yes:	Claims 1-13
	No:	Claims 14
Industrial applicability (IA)	Yes:	Claims 1-14
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Re Item V: Novelty, Inventive Step and Industrial Applicability (Art. 33(2) and (3) PCT)

1.1 Reference is made to the following document:

D1: CHANG HO NAM ET AL: 'High density cell culture membrane-based cell recycle.' BIOTECHNOLOGY ADVANCES, vol. 12, no. 3, 1994, pages 467- 487, XP000978939 ISSN: 0734-9750

1.2 Claim 14 is not new in view of document D1, thus not fulfilling the requirements of Art. 33(2) PCT. Claim 14 attempts to seek protection for a hollow fibre bioreactor, wherein the method of the preceding claims 1-13 is carried out.
In document D1, also a hollow-fibre bioreactor is disclosed that is used for high density cell culture. The same reactor can also be used for the application of the methods as claimed in the present application. The bioreactor is not rendered novel only because it is used in a special cell culture procedure. Moreover, it is an implicit technical feature of the hollow-fibre bioreactor of D1 that the methods of the present application can be carried out in said bioreactor, regardless if the method as such is novel and inventive. Beside this, hollow-fibre reactors are also known from WO9527040 and EP-A-0 317 874.

1.3 The prior art teaches only continuos cell culture systems in hollow-fibre reactors, for example for the cultivation of cell lines for the production of monoclonal antibodies or secondary metabolites. The difference of the present invention compared to the prior art lies in the infection of the cell line that is already in culture within the hollow-fibre reactor and the subsequent multiplying of infected cells, whereafter harvesting of the infected cells non-infected cell give rise to re-population of the reactor. The advantage of the present invention lies in the continuos culturing of the cell line followed by a greater productivity of the cells. The underlying technical problem lies in the provision of a method for continuously culturing cell lines that survive infections with lytic organisms that are capable of repopulating a bioreactor after harvesting infected cells. This problem has been solved by the present application. The prior art does not teach

the solution of the present invention. In consequence, the method of claims 1-13 fulfil the requirements of inventive step (Art.33(3) PCT).

1.4 Claims 1-14 fulfil the requirements of Industrial Applicability (Art.33(4) PCT).

2. Re Item VIII: Clarity (Art. 6 PCT)

2.1 Claims 1 lacks clarity as required by Art. 6 PCT, because the Applicant tries to define the subject matter for which protection is sought by the result to be achieved. Independent claim 1 does not contain all the technical features essential to the definition of the invention. From the reading of the claim the borders of the scope of the protected subject matter are not clear to the skilled person because of the vague wording, i.e. that the cell 'can' be harvested and 'can' survive.

2.2 It is clear from the description on pages 7-8 that the following features are essential to the definition of the invention:

(1) The stable cell line is capable of growing in the extra capillary space of the bioreactor to establish a population from at least 10e6 to10e9 cells per ml.
(2) At the point of infection with the lytic organism, the cell density will be 10e6 cell per ml.

2.3 Since independent claim 1 does not contain these features it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

2.4 The wording in claims 5 and 6, stating that the cell line 'can survive for at least' renders the scope of the claims unclear, because it gives the skilled person no clear technical teaching insofar, as it is also possible that the cells could also survive less than the time period given in the claims, which implies, that also cell lines which are not intended to fall under the scope of present claims, are included.